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14. ABSTRACT: This proposal focuses on development of a radically new method for breast magnetic resonance imaging (MRI), which could improve detection of small tumors and reduce the unnecessary biopsies generated by false positives in conventional breast MRI and mammography. This method is based on my groups recent discovery of a significant omission in the decades old theoretical framework of nuclear magnetic resonance (NMR, the spectroscopic precursor to MRI). We have shown that it is possible to detect strong signals from intermolecular resonances – for example, simultaneously flipping up a water spin at one location while flipping down another water spin 100 um away- even though such "intermolecular zero-quantum coherences" (iZQCs) would be predicted to be completely impossible to observe in the conventional formulation of NMR or MRI. This fundamentally new physics provides the basis for a potentially extremely useful contrast enhancement technique geared towards early detection and tumor grading. Our preliminary results demonstrated iZQC breast imaging on one healthy volunteer, with and without fat suppression. Unfortunately, the human approval process took the entire grant year, during which time the existing human machine was decommissioned. During this time, work progressed on phantom imaging and sequence improvement.

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Introduction

Work in my laboratory at the time of grant submission had shown that intermolecular cross-peaks could be generated in vivo, and that these peaks gave enhanced contrast in rat brain images, including tumor enhancement. These cross-peaks arise from dipolar couplings between distant spins in solution, which were previously thought to produce insignificant effects. Instead, we have shown (in five Science papers since 1993, among other places) that they lead to a completely new method for detecting small local variations in the resonance frequency. The overall goal of the research over the entire grant period is to demonstrate that we can enhance signal strength and specificity enough to make this a useful tool for clinical diagnosis of breast tumors. Work in the first grant period focused on transitions to human subjects, signal enhancement, and demonstration of contrast improvement; work in this grant period has focused on transitions to breast imaging, compensation for fat/water frequency difference (absent in brain imaging done to date), and optimization of contrast. Zero-quantum and double-quantum images in healthy subjects have now been demonstrated.

Body

The Statement of Work items relevant for this grant period (from the original proposal), and progress towards the stated goals, is listed below.

Task 1: Characterize intermolecular zero-quantum coherences in samples with susceptibility variations *in vitro*.

c. Develop enhanced imaging sequences (multiple echoes, fat suppression) and test in phantoms and on normal and tumor-containing tissue samples (months 3-36)

Progress on these items:

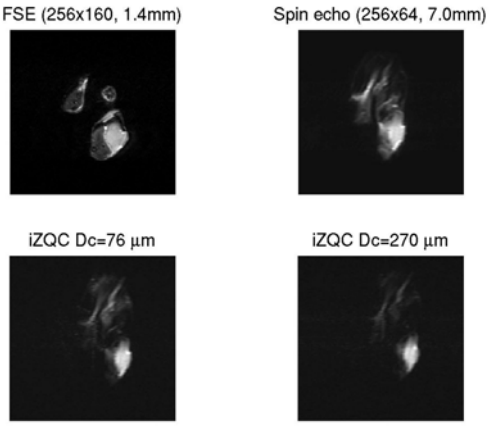


Figure 1. MRI studies were conducted on mice with tumors, to optimize parameters for iMQC imaging of breast cancers (after anticipated approval of human imaging protocols, which did not happen during the grant period). The figure above shows conventional images (fast spin echo and conventional spin echo) and zero-quantum images with different correlation distances. Differences between these images

c. Zero-quantum, double-quantum, and multiple echo sequences have been developed with fat suppression and with improved sensitivity. In all cases, the most serious issue with optimizing sequences for breast imaging is compensation for the susceptibility variations between fat and tissue. This was not an issue for brain imaging, but is particularly important in breast, and particularly complex for our sequences.

Sequences are developed for the 4T magnet at the University of Pennsylvania. In preparation for applications to breast tumors, we did some animal studies in conjunction with Harish Poptani and Jerry Glickson at Penn. Images of mouse RIF-1 tumors were acquired with iMQC and conventional T2-weighted sequences, and we concluded that the tumor to normal tissue contrast is larger for iMQC in some regions of the tumor. We also observed a strong dependence of tumor to normal tissue contrast with the choice of correlation distance. This work was presented at the BCRP review meeting in September 2002.

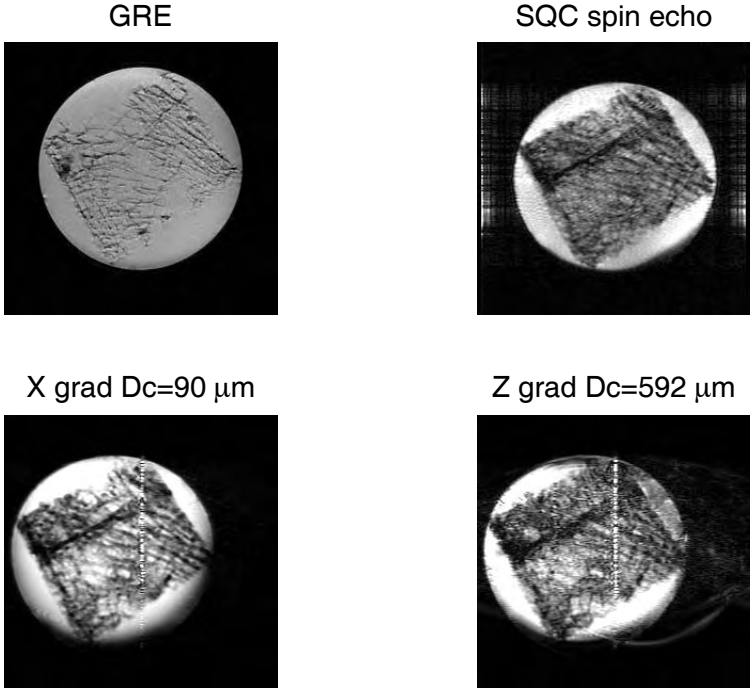


Figure 2. Studies of iZQC imaging in trabecular bone reveal substantial structure which is not presented in conventional T2* or T2 weighed imaging

We also conducted studies on trabecular bone, again looking for differences in image contrast between iMQC and conventional imaging. We did find such differences, and began to investigate parameters such as correlation distance and correlation direction dependence. This work looked promising, and led to an independent R21 NIH proposal. This work was also presented at the BCRP review in September 2002.

Task 2: Demonstrate breast MRI with contrast generated by intermolecular zero-quantum coherences

b. Include iZQC echo-planar studies in ongoing clinical protocols at the University of Pennsylvania on patients with known breast cancer at 4 Tesla (months 3-18)

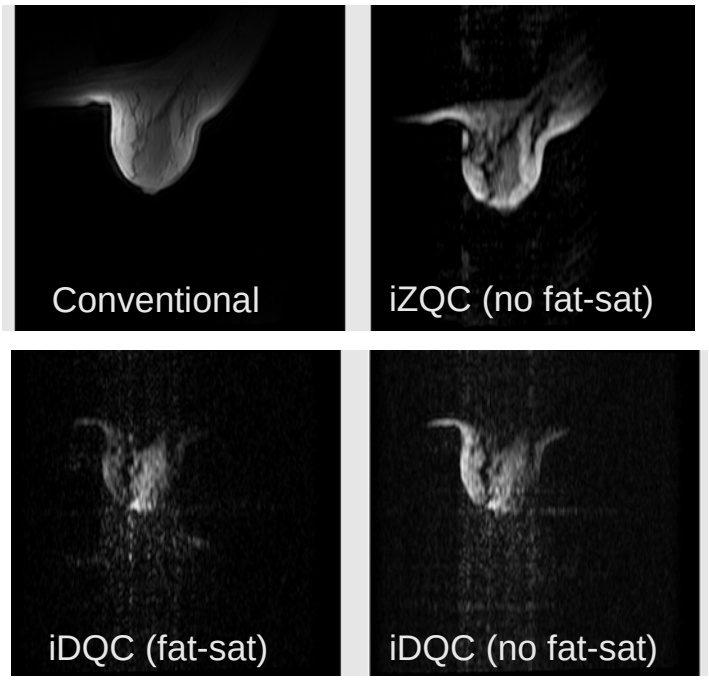
c. Develop data base of iZQC images to compare with conventional MRI, mammograms and biopsy results; evaluate correlations with iZQC signal intensity, linewidth, and nonexponential behavior (months 3-18)

d. Evaluate advanced iZQC imaging sequences at 1.5 Tesla on phantoms (months 12-15)

e. Include iZQC echo-planar studies in ongoing clinical protocols at the University of Pennsylvania on patients with known breast cancer at 1.5 Tesla, and compare with conventional MRI (months 12-24)

Progress: In the FY2001 report, we demonstrated iZQC and iDQC breast imaging on normal volunteers, including fat suppression (Figure 3, next page). The contrast differences are consistent with theoretical variations (and with Figure 2 above); for example, notice that boundaries between fat and surrounding tissue are enhanced. The images shown here were acquired in 6 minutes each. These images show motion artifacts which can be reduced by minor breast compression in the coil (far less than in a mammogram). For reasons we do not yet understand, the double-quantum images show more artifacts. Fat suppression is not yet working quite as well as it should; figure 3 uses a conventional fat suppression method (presaturation) which is fine in normal images, but which produced greater signal losses here.

This demonstration experiment was conducted with full IRB approvals, as an investigational procotol using instrumentation associated with the Metabolic Magnetic Resonance Research and Computational Center at the University of Pennsylvania. They are identical to conventional MR protocols, merely involving rearranging the order of a few gradient



Conventional image: (fast gradient echo, rf-spoiled): TR=150 ms, TE=1.6 ms, 5 mm thick, 256x128 matrix, FOV=24cm

iZQC/iDQC images: TR=3.5 s, TE=50 ms, 10 mm thick, 256x64, FOV=24 cm, t= 8 ms, 2 NEX (G_z-G_y subtraction), Gradient 2 G/cm * 3 ms (D_c = 197 um)

and radiofrequency pulses. However, we were informed by BCRP that a different set of approvals was needed for human subject research under this grant. The process of obtaining these approvals took almost all of the grant year; by the time the review process was completed, the instrument had been decommissioned for its scheduled replacement with a Siemens console. For this reason alone, human studies were not done in year 3.

Funding has been requested from the NIH to continue and extend these studies, in collaboration with an existing multimodality breast cancer detection trial at the University of Pennsylvania.

Task 3: Evaluate intermolecular multiple-quantum coherence contrast as a tool for breast cancer detection

a. As appropriate, test advanced pulse sequences on patients with no prior history of breast cancer and compare to other diagnostic methods (conventional MRI, mammography) (months 12-36).

Progress: task could not be completed due to restrictions imposed by BCRP on human subjects research.

It is worth noting that since that time, our NIH-funded work has in fact permitted us to continue development of intermolecular multiple-quantum coherence (iMQC) protocols related to breast cancer research. For example, the crosspeak between water and fat (commonly present in most voxels of a breast MR image) can be acquired quickly, and can serve as a measure of local temperature. We have also demonstrated that local anisotropy in iMQCs provides an addition measure of vascularity.

We have not resumed explicit breast MR imaging since the work was terminated by the Army review panel. The most recent experiments have been on fatty mice, which serve as an excellent substitute for breast tissue. It is likely that in the near future, we will be ready to adapt our sequences to clinical applications, now on GE scanners here at Duke University.

Key Research Accomplishments:

–Demonstrated iMQC and iZQC tumor contrast enhancement, and improved pulse sequences.

–Characterized advanced sequences for breast iZQC imaging

Reportable Outcomes:

Five conference papers were accepted dealing with the research done here.

Conclusions:

We have clearly demonstrated that the novel contrast mechanism we proposed for breast MR can be extended to human studies, with acceptable data acquisition times and enhanced contrast. Work is ongoing to prove that these methods actually give better images in breast.

References:

None in this report